Clinical Gastroenterology and Hepatology 2020;18:2650–2666

# NARRATIVE REVIEW

Fasiha Kanwal, Section Editor

## Contemporary Epidemiology of Chronic Liver Disease and Cirrhosis

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**BACKGROUND & AIMS:** **Accurate estimates for the contemporary burden of chronic liver disease (CLD) are vital for setting clinical, research, and policy priorities. We aimed to review the incidence, prevalence, and mortality of CLD and its resulting complications, including cirrhosis and hepatocellular carcinoma (HCC).**

**METHODS:** **We reviewed the published literature on the incidence, prevalence, trends of various etiologies of CLD and its resulting complications. In addition, we provided updated data from the Centers for Disease Control and Global Burden of Disease Study on the morbidity and mortality of CLD, cirrhosis, and hepatocellular carcinoma (HCC). Lastly, we assessed the strengths and weaknesses of available sources of data in hopes of providing important context to these national estimates of cirrhosis burden.**

**RESULTS:** **An estimated 1.5 billion persons have CLD worldwide and the age-standardized incidence of CLD and cirrhosis is 20.7/100,000, a 13% increase since 2000. Similarly, cirrhosis prevalence and mortality has increased in recent years in the United States. The epidemiology of CLD is shifting, reflecting implementation of large-scale hepatitis B vaccination and hepatitis C treatment programs, the increasing prevalence of the metabolic syndrome, and increasing alcohol misuse.**

**CONCLUSIONS:** **The global burden of CLD and cirrhosis is substantial. Although vaccination, screening, and antiviral treatment campaigns for hepatitis B and C have reduced the CLD burden in some parts of the world, concomitant increases in injection drug use, alcohol misuse, and metabolic syndrome threaten these trends. Ongoing efforts to address CLD-related morbidity and mortality require accurate contemporary estimates of epidemiology and outcomes.**

*Keywords:* Alcohol-related; Hepatitis B; Liver Cancer; Hepatitis C; Nonalcoholic Fatty Liver Disease.

Chronic liver disease (CLD) and cirrhosis account for >44,000 deaths in the United States and 2 million deaths worldwide each year, in addition to a high burden of disability and increased health care utilization.[1,2] However, mortality estimates for CLD likely are conservative and underestimate its true burden.[3] The most common etiologies of CLD and cirrhosis are chronic hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-related liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD). Multiple recent developments are reshaping the epidemiology of CLD and cirrhosis including neonatal HBV vaccination campaigns, improved HCV treatment access and effectiveness, the opioid crisis, the obesity epidemic, and increasing rates of alcohol misuse.

Accurate estimates of the contemporary burden of cirrhosis are vital for setting clinical, research, and policy priorities. In light of the ever-changing nature of CLD epidemiology, we aimed to review the global incidence, prevalence, and mortality of CLD and its resulting

*Abbreviations used in this paper:* ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ALD, alcohol-related liver disease; CLD, chronic liver disease; DAA, direct acting antiviral; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Survey; PBC, primary biliary cholangitis; VA, Veterans Affairs.

Most current article

© 2020 by the AGA Institute
1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2019.07.060

complications including cirrhosis and hepatocellular carcinoma (HCC).

## Incidence, Prevalence, and Mortality of Chronic Liver Disease

### *Global Burden of Chronic Liver Disease*

Globally, 1.5 billion persons had CLD in 2017, most commonly resulting from NAFLD (60%), HBV (29%), HCV (9%), and ALD (2%).[4] In European countries, the median cirrhosis prevalence was 833 of 100,000 (range, 447–1100), but data on cirrhosis prevalence in other areas, particularly resource-limited settings, are sparse.[5,6] Similarly, accurate accounting of cirrhosis and CLD incidence is difficult in most areas because of a paucity of high-quality, prospective data.[6] Based on data from the Global Burden of Disease study, the age-standardized incidence rate of cirrhosis and CLD was 20.7 per 100,000 in 2015, a 13% increase from 2000 (Tables 1 and 2).[7] The estimated incidence of cirrhosis in Europe is 26.0 per 100,000, and the incidence in Asia ranges from 16.5 per 100,000 in East Asia to 23.6 per 100,000 in Southeast Asia.[7]

There have been small increases in cirrhosis incidence in Europe, high-income Asia-Pacific, East Asia, Southeast Asia, and South Asia from 2000 to 2015.[7] Although HBV vaccination and viral hepatitis treatment programs have curbed the incidence of cirrhosis in many countries, including Japan and Taiwan, the increasing burden of obesity, metabolic syndrome, and alcohol misuse threatens these trends.[7–9]

The major complications of CLD—cirrhosis (1.2 million deaths) and liver cancer (790,000 deaths)—account for 3.5% of all deaths worldwide.[10] In Figure 1 we detail the global age-adjusted mortality per 100,000 persons across regions. Cirrhosis-related mortality decreased from 20.0 per 100,000 person-years in 1980 to 15.8 per 100,000 person-years in 2010.[1] Although decreased mortality rates were pronounced in East Asia, North Africa/Middle East, and high-income Asia Pacific, increases in mortality were observed in many other parts of the world including South Asia, Central Asia, and Eastern Europe. These disparate trends likely are related to differences in the distribution of underlying CLD etiologies and strategies to curb CLD burden. Deaths from cirrhosis increased 2-fold in sub-Saharan Africa between 1980 and 2010, primarily owing to viral hepatitis and ALD.[1] Although viral hepatitis remains the driving force behind cirrhosis-related mortality in Asia, deaths are decreasing because of increased HBV vaccination and treatment of viral hepatitis.[1,11,12] ALD currently is responsible for most cirrhosis-related deaths in Europe, but trends vary between countries, with mortality decreasing in some countries (Austria, Denmark, France, Germany, and Hungary) and increasing in others (Finland, Ireland, United Kingdom).[9] Beyond mortality, disability is another metric of morbidity. We therefore detail in Figure 2 the years lost to disability attributed to cirrhosis.

### *Burden of Chronic Liver Disease in North America*

Estimates detailing the epidemiology of CLD in North America also are limited by the paucity of longitudinal, population-based data. Baby boomers (born 1945–1965) comprise half of cirrhosis cases in North America, with a relatively higher prevalence among blacks, Hispanics, and those with lower levels of education.[13–15] The estimated prevalence of cirrhosis ranges from 300 to 1000 per 100,000, conditional on the variable risk of CLD across populations (Table 2).[13–15] For example, the estimated incidence of cirrhosis is 167 per 100,000 person-years within the US Veterans Affairs (VA) system compared with 90 per 100,000 person-years in a population from Ontario, Canada.[13,14] These discrepant estimates may be explained by ascertainment bias or differences in the patient populations, including the VA's predominantly male population with a higher burden of viral hepatitis, alcohol misuse, and metabolic syndrome.[16,17]

The prevalence of cirrhosis has increased 1.5- to 2-fold over the past 2 decades.[13–15] Although most prevalent cirrhosis cases are in the baby boomer cohort, incident cirrhosis diagnoses are highest and increasing disproportionately in younger Americans.[13,14] As reflected in a Canadian population-based cohort in whom risk factors such as metabolic syndrome and alcohol misuse are increasing among young people, age-specific cirrhosis incidence increased 22% from 1997 to 2016.[13]

After several decades of stability from 1970 to 2008, CLD-related mortality has since increased steadily, with disproportionate relative increases among young people, women, non-Hispanics, whites, and Native Americans.[2,3] Following a National Center for Health Statistics study that showed a 65% increase in cirrhosis mortality from 2009 to 2016, we present updated statistics through 2017 (Table 3).[2] Age-adjusted mortality rates from CLD and cirrhosis continued to increase, with estimates of 14.2 (95% CI, 14.0–14.3) and 9.2 (95% CI, 9–1-9.3) per 100,000, respectively, in 2017 (Figure 3).

## Specific Chronic Liver Diseases

The relative contribution of viral hepatitis, NAFLD, and ALD to the global burden of CLD rapidly is shifting.[4,7,8,18,19] Globally, HBV incidence and its complications have been reduced by widespread vaccination and antiviral treatment programs. In contrast, although many patients with chronic HCV infection are being treated successfully with direct acting antiviral (DAA) therapy, reducing future risk of developing cirrhosis or HCC,[20] the opioid epidemic and intravenous drug use patterns have resulted in an increased number of acute

**Table 1.** Prevalence, Incidence, Mortality, and Costs of CLD and Cirrhosis Globally

| Study | Country/region | Prevalence, per 100,000 population[a] | Incidence, per 100,000 person-years[a] | Mortality, per 100,000 person-years[a] | Costs |
|---|---|---|---|---|---|
| Cirrhosis | | | | | |
| Global Burden of Disease,[4] 2018 | All | Cirrhosis and CLD, 1.5 billion (2017)[a] | Cirrhosis and CLD, 5.2 million (2017)[a] | – | Cirrhosis and CLD YLDs 1.8 million (2017) |
| Mokdad (2014)[1] | All | – | – | 15.7 (2010) | – |
| Mokdad et al,[1] 2014 | Asia | – | – | 8.2–33.7 (2010) | – |
| Mokdad et al,[1] 2014 | Europe | – | – | 10.2–20.0 (2010) | – |
| Mokdad et al,[1] 2014 | Latin America | – | – | 15.8–27.5 (2010) | – |
| Mokdad et al,[1] 2014 | North Africa/Middle East | – | – | 20.2 (2010) | – |
| Mokdad et al,[1] 2014 | Oceania | – | – | 41.5 (2010) | – |
| Mokdad et al,[1] 2014 | Sub-Saharan Africa | – | – | 12.9–24.2 (2010) | |
| Ratib et al,[162] 2017 | United Kingdom | – | 35.9 (2009) | 5.9 (2009) | |
| HCV | | | | | |
| WHO et al,[24] 2017 | All | 1000 (2015) | 23.7 (2015) | 402,000 (2015)[a] | – |
| WHO et al,[24] 2017 | Africa | 1000 (2015) | 31.0 (2015) | – | – |
| WHO et al,[24] 2017 | Eastern Mediterranean | 2300 (2015) | 62.5 (2015) | – | – |
| WHO et al,[24] 2017 | Europe | 1500 (2015) | 61.8 (2015) | – | – |
| WHO et al,[24] 2017 | Americas | 700 (2015) | 6.4 (2015) | – | – |
| WHO et al,[24] 2017 | South-East Asia | 500 (2015) | 14.8 (2015) | – | – |
| WHO et al,[24] 2017 | Western Pacific | 700 (2015) | 6.0 (2015) | – | – |
| HBV | | | | | |
| WHO et al,[24] 2017 | All | 3500 (2015) | 1300 (age, <5 y) (2015) | 884,000 (2015)[a] | – |
| WHO et al,[24] 2017 | Africa | 6100 (2015) | 3000 (age, <5 y) (2015) | – | – |
| WHO et al,[24] 2017 | Eastern Mediterranean | 3300 (2015) | 1600 (age, <5 y) (2015) | – | – |
| WHO et al,[24] 2017 | Europe | 1600 (2015) | 400 (age, <5 y) (2015) | – | – |
| WHO et al,[24] 2017 | Americas | 700 (2015) | 200 (age, <5 y) (2015) | – | – |
| WHO et al,[24] 2017 | South-East Asia | 2000 (2015) | 700 (age, <5 y) (2015) | – | – |
| WHO et al,[24] 2017 | Western Pacific | 6200 (2015) | 900 (age, <5 y) (2015) | – | – |
| NAFLD | | | | | |
| Global Burden of Disease,[4] 2018 | All | NASH cirrhosis 11,061 (2017) | – | – | – |
| Younossi et al,[53] 2015 | All | 25,000 | – | – | – |
| Younossi et al,[53] 2015 | Africa | 13,500 | – | – | – |
| Li et al,[54] 2019 | Asia | 33,900 (2012–2017) | 5090 (1999–2019) | | |
| Wong et al,[59] 2015 | Hong Kong | – | 3400 (2008–2013) | – | – |
| Zhou et al,[58] 2011 | China | – | 9100 (2009) | – | – |
| Chang et al,[61] 2016 | South Korea | | 2970 (2002–2013) | | |
| Younossi et al,[53] 2015 | Europe | 23,710 | – | – | – |
| Younossi et al,[163] 2016 | Germany, France, Italy, United Kingdom | – | – | – | €35 billion direct costs (€354–1163 per patient) |
| Kanerva (2014)[164] | Finland | 41,150 | – | – | – |
| Zelber-Sagi (2014)[60] | Israel | – | 2714 (2003–2010) | – | – |
| Younossi et al,[53] 2015 | Middle East | 31,790 | – | – | – |
| Younossi et al,[53] 2015 | South America | 30,450 | – | – | – |
| Riquelme et al,[165] 2009 | Chile | 23,400 | – | – | – |
| ALD | | | | | |
| Global Burden of Disease,[4] 2018 | All | 26 million (2017)[a] | 903,700 annually (2017)[a] | – | YLDs, 400,100 |
| Rehm et al,[67] 2013 | All | – | – | 7.2 (2010) | – |
| HCC | | | | | |
| Global Burden of Disease,[4,101] 2017/2018 | All | 803,400 (2017)[a] | 953,100 annually (2017)[a] | 12.1 (2015) | YLDs, 229,500 (2017) |

NOTE. Empty cells is due to data not being available.
ALD, alcohol-related liver disease; CLD, chronic liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; WHO, World Health Organization; YLD, years lost to disability.
[a]If the total population was unavailable, the total number of cases is shown.

**Table 2.** Prevalence, Incidence, Mortality, and Costs of CLD and Cirrhosis in North America

| Study | Data source | Prevalence, per 100,000 population | Incidence, per 100,000 person-years | Mortality, per 100,000 person-years | Costs |
|---|---|---|---|---|---|
| Cirrhosis | | | | | |
| Beste et al,[14] 2015 | US VA system | 1058 (2013) | 167 (2012) | 126 (2013) | – |
| Flemming et al,[13] 2018 | Routinely collected health data from Ontario, Canada | 840 (2016) | 90 (2016) | – | – |
| Scaglione et al,[15] 2015 | NHANES | 302 (2010) | – | 2-year mean proportion of deaths, 26.4% (1999–2006) | – |
| Mellinger et al,[70] 2018 | Truven Marketscan Commercial Claims and Encounters Database (Ann Arbor, MI, Chicago, IL, and Denver, CO) | 270 (2015) | – | – | – |
| Tapper and Parikh,[2] 2018 | CDC | – | – | 12.2 (1999–2016) | – |
| HCV | | | | | |
| CDC,[27] 2018 | National notifiable diseases surveillance system | – | 1.0 (2016) | 4.5 (2016) | – |
| Hofmeister et al,[21] 2019 | NHANES | 900 (2013–2016) | | | |
| Beste et al,[14] 2015 | US VA system | HCV cirrhosis, 503 (2013) | HCV cirrhosis, 77.9 (2012) | – | – |
| HBV | | | | | |
| CDC,[27] 2018 | National notifiable diseases surveillance system | – | 1.0 (2016) | 0.5 (2016) | – |
| Roberts et al,[166] 2016 | NHANES | 300 (2012) | – | – | – |
| Beste et al,[14] 2015 | US VA system | HBV cirrhosis, 503 (2013) | HBV cirrhosis, 3.3 (2012) | | |
| NAFLD | | | | | |
| Browning et al,[56] 2004 | Dallas Heart Study | 34,000 | | | |
| Kanwal et al,[16] 2016 | US VA system | 17,610 (2011) | 2500 (2011) | – | – |
| Allen et al,[51] 2018 | Olmsted County, Minnesota | – | 329 (2014) | – | – |
| Younossi et al,[163] 2016 | Markov model | – | – | – | $103 billion direct costs ($1613 per patient) |
| Beste et al,[14] 2015 | US VA system | NASH cirrhosis, 161 (2013) | NASH cirrhosis: 30.3 (2012) | – | – |
| Kabbany et al,[50] 2017 | NHANES | NASH cirrhosis, 178 (2009–2012) | | | |
| ALD | | | | | |
| Mellinger et al,[70] 2018 | Truven Marketscan Commercial Claims and Encounters Database | Alcoholic cirrhosis, 100 (2015) | – | – | $44,835 per-person (alcoholic cirrhosis) vs $23,319 per-person (nonalcoholic cirrhosis) |
| Beste et al,[14] 2015 | US VA system | Alcoholic cirrhosis, 327 (2013) | Alcoholic cirrhosis, 47.8 (2012) | – | – |
| HCC | | | | | |
| White et al,[107] 2017 | US Cancer Statistics registry | – | 6.7 (2012) | – | – |
| Altekruse et al,[105] 2014 | SEER/CDC | – | 5.9 (2006–2010) | 4.3 (2006–2010) | – |
| Tapper and Parikh,[2] 2018 | CDC | – | – | 3.6 (1999–2016) | – |

ALD, alcohol-related liver disease; CDC, Centers for Disease Control and Prevention; CLD, chronic liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Survey; SEER, Surveillance Epidemiology, and End Results; VA, Veterans Affairs.

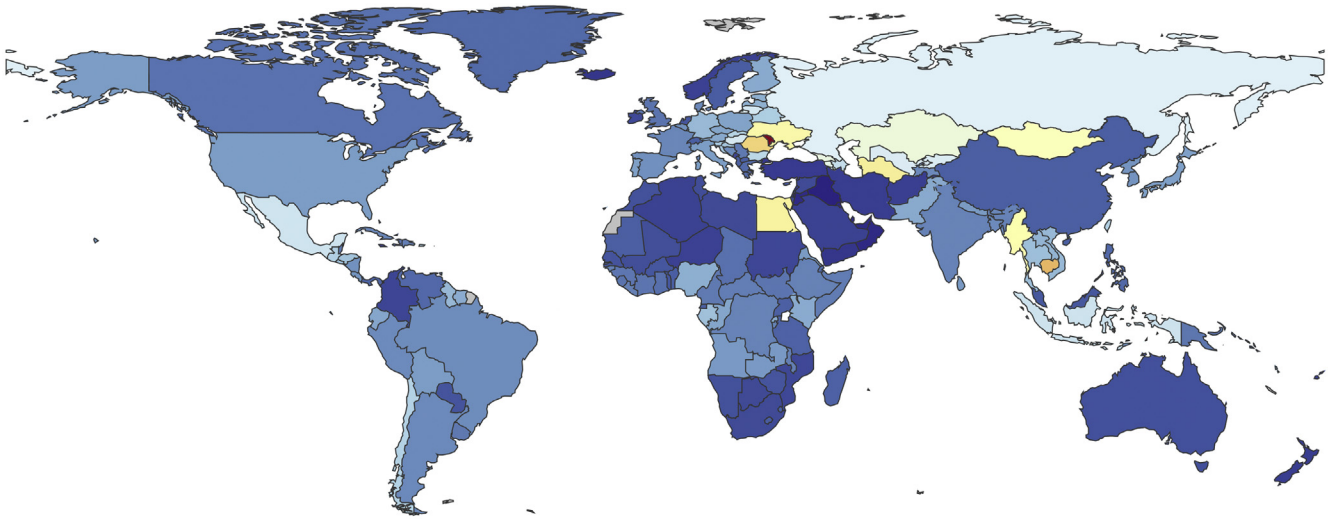

**Figure 1.** Global burden of cirrhosis mortality. The age-adjusted risk of mortality (per 100,000 persons) attributed to cirrhosis is shown. Legend (mortality per 100,000 persons): dark to light blue (0–40), yellow (40–50), yellow-orange (50–60), orange-red (60–70), and red (>70). Adapted from the Global Burden of Disease Study.[167]

HCV infections.[21] In parallel, NAFLD is becoming an increasingly important cause of CLD worldwide, concurrent with an increasing burden of obesity and metabolic syndrome. Similarly, alcohol consumption is responsible for an estimated 27% of liver-related deaths worldwide, with the highest rates of mortality in Europe, and has been increasing in many countries globally.[22]

### *Hepatitis C Virus Infection*

Approximately 71 million people worldwide (1.0%) have chronic HCV, with a prevalence of 1.0% in the United States, 1.5% to 1.8% in Europe, 1.0% in Africa, and 0.5% to 0.7% in Asia.[23–26] Most HCV infections are caused by genotypes 1 and 3, which are estimated to account for 44% and 25% of infections, respectively.[26] There are an estimated 1.8 million new HCV infections per year (incidence rate, 23.7 per 100,000), with the highest rates in the Eastern Mediterranean (62.5 per 100,000) and Europe (61.8 per 100,000).[24] In the United States, an estimated 41,200 new HCV infections occurred in 2016 (incidence rate, 13.9 per 100,000).[27] In contrast to other infectious diseases, including human immunodeficiency virus, malaria, and tuberculosis, deaths from viral hepatitis have been increasing over the past 15 years.[28] HCV has been a leading cause of cirrhosis and HCC, accounting for an estimated 400,000 liver-related deaths worldwide in 2015.[24]

Highly effective DAAs were introduced in 2014 and have increased treatment eligibility and success dramatically. The US VA system, Egypt, Republic of Georgia, and Iceland are prime examples of success for large-scale screening, antiviral treatment, and micro-elimination efforts.[17,29–33] However, the potential benefit of DAAs has been blunted by incomplete HCV screening and linkage to care, particularly in rural and

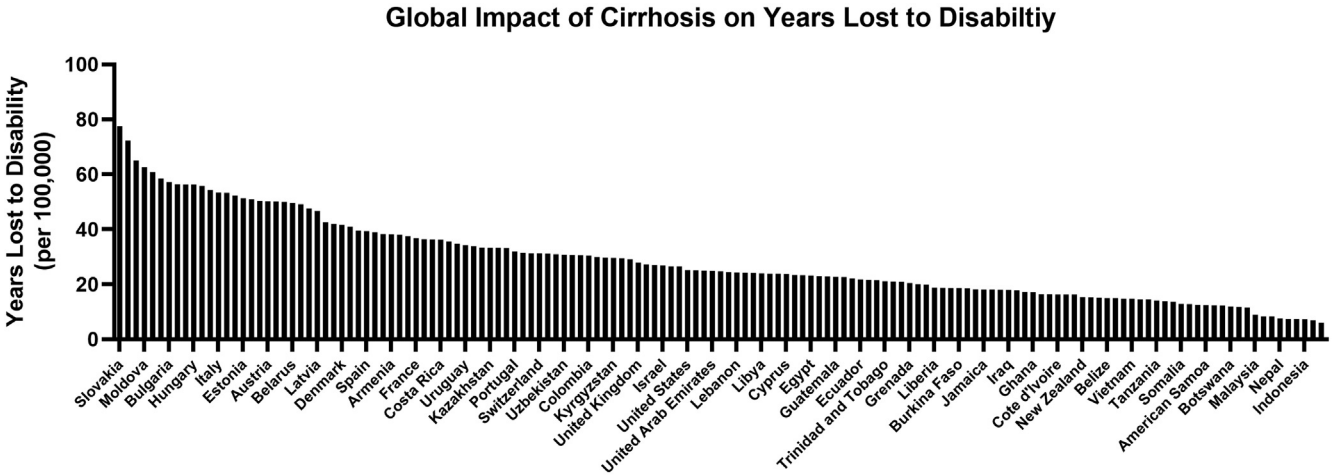


**Figure 2.** Global burden of years lost to disability (YLD) as a result of cirrhosis is shown. YLD is a function of the disease incidence, the disability weight (on functioning), and the average duration of illness. Adapted from the Global Burden of Disease Study.[167]

**Table 3.** Mortality From CLD, Cirrhosis, and HCC in the United States, Overall and Among Various Subgroups From 1999 to 2017

| | Combined liver-related mortality rate/100,00 (95% CI) | CLD mortality rate/100,000 (95% CI) | Cirrhosis mortality rate/100,000 (95% CI) | HCC mortality rate/100,000 (95% CI) |
|---|---|---|---|---|
| Overall | 15.20 (15.16–15.23) | 12.86 (12.84–12.89) | 7.96 (7.94–7.98) | 2.34 (2.33–2.35) |
| Sex | | | | |
| Female | 10.04 (10.00–10.07) | 9.06 (9.03–9.09) | 5.27 (5.25–5.30) | 0.97 (0.96–0.98) |
| Male | 21.04 (20.99–21.09) | 17.10 (17.05–17.15) | 10.96 (10.93–11.00) | 3.92 (3.90–3.95) |
| Age, *y* | | | | |
| 25–34 | 1.81 (1.78–1.84) | 1.71 (1.69–1.74) | 0.73 (0.71–0.75) | 0.10 (0.09–0.11) |
| 35–44 | 8.53 (8.47–8.60) | 8.18 (8.11–8.24) | 4.62 (4.57–4.67) | 0.36 (0.35–0.37) |
| 45–54 | 26.15 (26.04–26.27) | 23.56 (23.46–23.67) | 14.68 (14.59–14.76) | 2.59 (2.56–2.63) |
| 55–64 | 42.33 (42.17–42.49) | 34.95 (34.81–35.10) | 22.28 (22.16–22.39) | 7.37 (7.30–7.44) |
| 65–74 | 47.73 (47.52–47.94) | 38.53 (38.34–38.72) | 24.79 (24.64–24.94) | 9.21 (9.11–9.30) |
| 75–84 | 53.68 (53.39–53.96) | 42.15 (41.89–42.40) | 27.16 (26.96–27.37) | 11.53 (11.40–11.66) |
| ≥85 | 46.30 (45.88–46.72) | 37.32 (36.94–37.70) | 21.17 (20.88–21.45) | 8.98 (8.80–9.17) |
| Race | | | | |
| Native American | 33.00 (32.51–33.49) | 29.89 (29.42–30.35) | 16.93 (16.59–17.28) | 3.12 (2.96–3.29) |
| Asian/Pacific Islander | 9.70 (9.57–9.82) | 4.96 (4.87–5.05) | 2.90 (2.83–2.97) | 4.76 (4.67–4.84) |
| Black | 14.40 (14.31–14.49) | 10.99 (10.91–11.07) | 6.29 (6.23–6.35) | 3.43 (3.38–3.47) |
| White | 15.20 (15.16–15.23) | 13.31 (13.28–13.34) | 8.33 (8.31–8.36) | 2.06 (2.05–2.07) |
| Ethnicity | | | | |
| Hispanic | 22.08 (21.95–22.21) | 18.33 (18.21–18.45) | 12.49 (12.39–12.59) | 3.74 (3.69–3.80) |
| Non-Hispanic | 14.56 (14.53–14.59) | 12.33 (12.30–12.36) | 7.52 (7.50–7.54) | 2.22 (2.20–2.23) |
| Geographic region | | | | |
| Northeast | 12.97 (12.91–13.04) | 10.71 (10.65–10.77) | 6.38 (6.33–6.43) | 2.28 (2.25–2.30) |
| Midwest | 13.71 (13.65–13.77) | 11.69 (11.63–11.75) | 7.08 (7.03–7.12) | 2.00 (1.98–2.03) |
| South | 16.16 (16.11–16.21) | 13.82 (13.78–13.87) | 8.85 (8.81–8.89) | 2.31 (2.29–2.33) |
| West | 15.20 (15.16–15.23) | 14.24 (14.18–14.30) | 8.71 (8.66–8.76) | 2.79 (2.76–2.82) |

NOTE. Data are from the Centers for Disease Control and Prevention National Center for Health Statistics.
Age-adjusted rates are listed for all categories with the exception of age strata. Combined liver-related definition: C22.0, K70, K71, K72, K73, K74, K75, K76; cirrhosis mortality definition: K74.6, K74.5, K70.3; CLD mortality definition: K70, K71, K72, K73, K74, K75, K76; and HCC mortality definition: C22.0.
CLD, chronic liver disease; HCC, hepatocellular carcinoma.

socioeconomically disadvantaged areas.[34] Despite recommendations for HCV screening in at-risk individuals in many countries, an estimated 80% of chronic HCV infections remain undiagnosed worldwide, ranging from 94% in Africa to 68% in the Americas.[35] Even among patients who undergo HCV screening, there are suboptimal rates of confirmatory HCV RNA testing and linkage to care.[36] Finally, HCV treatment often is not covered by insurance or is withheld for high-risk groups such as those who inject drugs, potentially as a result of

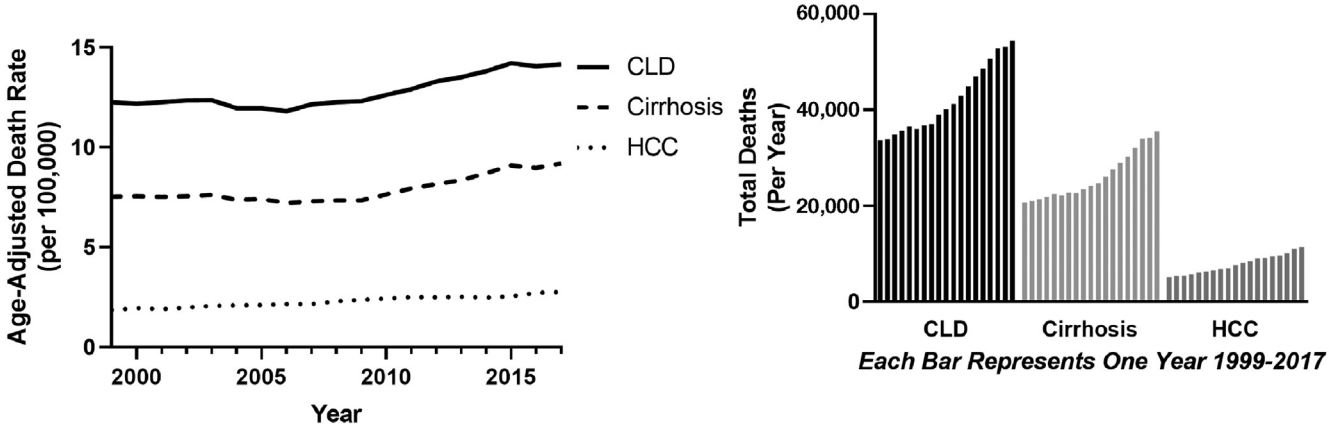


**Figure 3.** Mortality resulting from chronic liver disease (CLD), cirrhosis, and hepatocellular carcinoma (HCC) in the United States (from 1999 to 2017). The age-adjusted mortality for CLD, cirrhosis, and HCC has changed over time (*left*). Although HCC-related mortality has increased slowly since 1999, mortality as a result of CLD and cirrhosis began increasing after 2008, continuously through 2017. The raw numbers of deaths attributed primarily to CLD, cirrhosis, and HCC for each year from 1999 to 2017 are shown (*right*).

abstinence requirements from some payers, despite professional society guidance statements recommending otherwise.[37–39]

Worldwide, the number of newly infected individuals (1.75 million) exceeds the sum of patients dying from HCV (399,000) and those being treated successfully and cured (843,000).[24,35] Injection drug use accounts for increasing numbers of HCV infections in the United States, particularly among those who reside in rural areas, aged 20 to 29 years, and are non-Hispanic white.[27,40–42] HCV seroprevalence is now higher among young adults than baby boomers in several areas of the United States.[43] Unfortunately, the rapidly changing policy landscape and shifting trends described earlier render data inadequate even after 1 year, limiting our understanding of true contemporary HCV prevalence.[17]

### *Chronic Hepatitis B Virus Infection*

Worldwide, 257 million (3.5%) people had chronic HBV infection in 2015.[5,24,44] Western Pacific nations (6.2%) and Africa (6.1%) had the highest prevalence of HBV and accounted for more than two thirds of all cases.[24] A recent survey from the National Health and Nutrition Examination Survey (NHANES) estimated the US prevalence of chronic HBV as 840,000 (0.35%) overall in 2011 to 2016, varying from 3.85% among Asian immigrants and 0.79% among American-born Asians.[45]

Encouraging trends in HBV incidence have resulted from large-scale neonatal vaccination efforts in many countries.[5,46] Vaccination is particularly important for the estimated 65 million women of childbearing age with chronic HBV.[24] Worldwide, HBV prevalence among children younger than age 5 years (a surrogate of HBV incidence) has decreased from 4.7% in the pre-HBV vaccination era (1980s–2000s) to 1.3% in 2015. Improvements in vaccination coverage and subsequent decreases in childhood HBV infection have been seen specifically in South East Asia, Western Pacific, and the Eastern Mediterranean region.[7,24,47] However, HBV vaccination coverage remains low in some regions, particularly in Africa, and coverage with the initial birth vaccination dose continues to lag (<40%).[24] Beyond vaccination programs, efforts to curb HBV mortality are limited by inadequate diagnosis and treatment of chronically infected patients, partly owing to the lack of uniform HBV treatment guidelines, poor awareness of active infection (15.2% in 1 US study), and limited access to risk-assessment tools such as noninvasive tests for fibrosis.[35,45,48] Overall, among the estimated 250 million individuals with chronic HBV, 10% were aware of their diagnosis and 2% were currently on treatment.[49]

### *Nonalcoholic Fatty Liver Disease*

NAFLD encompasses a spectrum including hepatic steatosis, nonalcoholic steatohepatitis (NASH), and cirrhosis. Although accurate estimates of NAFLD are difficult to obtain, it is likely a major driver of the increasing cirrhosis incidence, concordant with trends in obesity and metabolic syndrome.[16,50,51] The pitfalls of NAFLD epidemiology relate primarily to the staging of disease. Hepatic steatosis in the absence of other causes (eg, significant alcohol use) can be estimated among cohorts receiving abdominal imaging or liver enzyme testing; NASH, a histologic diagnosis, can be estimated only from cohorts including biopsy data or self-reported diagnoses[52]; cirrhosis can be estimated from cohorts with adequate laboratory, histology, or imaging data.

The global prevalence of NAFLD is estimated at approximately 24%, with considerable variability from Africa (13.5%) to South America (30.5%), the Middle East (31.8%), and Asia (33.9%).[53,54] Approximately 1 in 3 US residents has hepatic steatosis and it is seen more commonly in Hispanics, followed by whites and blacks.[55,56] Based on the prevalence of biopsy-proven NASH in patients with NAFLD (6.7%–29.9%), it is estimated that approximately 1.5% to 6.5% of the general US population has NASH.[53] A study from 5 European countries estimated the prevalence of NASH at 0.29% using self-reported diagnoses.[52] An estimated 178 of 100,000 Americans have NASH cirrhosis based on data from NHANES, and its prevalence has increased 2.5-fold from 1999 to 2002 to 2009 to 2012.[50] There are also significant ethnic and racial disparities in the prevalence and severity of NAFLD in the US.[55]

Population-based, longitudinal data to track NAFLD incidence are lacking in many places. In studies with varying case definitions and populations, the reported incidence of hepatic steatosis per 100,000 person-years has ranged from 1850 in Italy, 2714 in Israel, 3400 in Hong Kong, 5090 in Asia, and 9100 in China.[54,57–61] A population-based study in Minnesota reported that the age- and sex-adjusted NAFLD incidence, defined by diagnostic codes, was 317 per 100,000 person-years. This is considerably lower than the estimated NAFLD incidence of 2500 per 100,000 person-years reported in the US VA system, in which cases were defined by increased liver enzyme levels without viral hepatitis or significant alcohol use.[16,51]

The increasing burden of obesity in children is particularly concerning given its association with the future development of NAFLD, cirrhosis, and HCC.[62–64] It is estimated that the pooled mean prevalence of NAFLD in children is 7.6% overall and 34.2% in obese children, with a higher prevalence in males compared with females.[65] Computer simulations based on the current estimates of NAFLD, obesity, and diabetes project that, from 2015 to 2030, the prevalence of NAFLD and NASH will increase by 21% and 63%, respectively.[66] In addition, the prevalence of NAFLD-related decompensated cirrhosis, HCC, and deaths will increase by 168%, 137%, and 178%, respectively.

### Alcohol-Related Liver Disease

ALD encompasses alcoholic hepatitis, steatosis, steatohepatitis, and fibrosis/cirrhosis. A lack of accurate reporting and referral bias limit the ability to estimate ALD incidence and prevalence globally, but alcohol misuse is responsible for an estimated 27% of deaths from liver disease and 30% of liver cancer deaths worldwide.[67–69] In the United States, the prevalence of ALD is estimated to be 4.7%, and alcohol is estimated to account for approximately 20% (NHANES) to 36% (private-insurance claims data) of cirrhosis cases.[15,70–72] Hispanics have a higher prevalence of ALD cirrhosis (16.9 per 100,000) compared with whites (11.1 per 100,000) or blacks (9.9 per 100,000).[73]

The relationship between alcohol use and liver disease is well established, with prospective cohorts showing that cirrhosis incidence is strongly related to the amount of alcohol consumed.[74,75] The estimated burden of ALD therefore can be estimated indirectly by alcohol consumption patterns. An estimated 2.3 billion people drink alcohol worldwide, and alcohol is consumed by more than half the population in the Americas, Europe, and the Western Pacific.[71] The highest per-capita alcohol consumption levels are observed in Eastern Europe (8.1 L/women, 24.9 L/men) and are lowest in North Africa/Middle East (0.2 L/women, 1.7 L/men).[67] Existing data suggest that ALD prevalence is increasing. In China, the proportion of all hospitalizations for liver disease attributable to alcohol more than doubled from 2002 to 2013.[76] Population-based data from Denmark have shown that the incidence of hospitalizations for alcoholic hepatitis increased from 1999 to 2008.[77] Similarly, the prevalence of alcohol-related cirrhosis in North America is increasing, particularly among young persons.[13,14,70,78] The global burden of ALD may continue to escalate given increases in alcohol consumption worldwide (per-capita consumption from 5.5 L in 2005 to 6.4 L in 2016).[79,80]

### Other Chronic Liver Disease Etiologies

Primary biliary cholangitis (PBC) occurs primarily in women and has a reported annual prevalence and incidence of 1.9 to 40.2 and 0.3 to 5.8 per 100,000, respectively.[81–83] In a systematic review of PBC, all longitudinal studies identified reported increases in PBC prevalence over time.[83] Similarly, data from a multicenter PBC consortium within the United States showed a stable incidence (4.2–4.3 per 100,000 person-years) and an increasing prevalence (21.7–39.2 per 100,000 population) from 2006 to 2014.[84] PBC is diagnosed at earlier stages over time, suggesting additional data are needed to understand longitudinal differences in its prevalence in the context of widespread antimitochondrial antibody test utilization.[85]

Similar to PBC, most studies on the epidemiology of primary sclerosing cholangitis come from North America and Europe. The reported prevalence of primary sclerosing cholangitis ranges from 0 to 16.2 per 100,000 person-years and its incidence ranges from 0 to 1.3 per 100,000.[83] Prevalence estimates vary from zero cases among Alaskan Natives[82] to higher estimates from the United Kingdom (12.7 per 100,000), general US population (13.6 per 100,000), and Sweden (16.2 per 100,000).[86–88] The incidence of primary sclerosing cholangitis is slowly increasing in populations in both North America and Europe.[83]

Epidemiologic data on autoimmune hepatitis are scant and there are no population-based data from the United States. It occurs primarily in women and its prevalence has been reported to be 4 per 100,000 in Singapore and 16 to 24 per 100,000 in Europe.[89–93] The annual incidence of autoimmune hepatitis has been reported to be 0.7 per 100,000 in Israel and 2.0 per 100,000 in New Zealand.[92,93] In Denmark, the incidence of autoimmune hepatitis nearly doubled from 1994 to 2012.[89]

Although hereditary hemochromatosis mutations are relatively common, particularly in Northern Europeans, C282Y homozygosity is weakly penetrant, rarely developing clinical manifestations (<1%), making it a rare cause of CLD.[94–97] Wilson disease also occurs infrequently (worldwide prevalence, 3 per 100,000), although a recent study from the United Kingdom reported a higher prevalence of individuals carrying 2 mutant pathogenic ATP7B alleles (14 per 100,000).[98] This apparent discrepancy may reflect the incomplete penetrance of ATP7B mutations or underdiagnosis. The prevalence of Wilson disease among patients who are undergoing evaluation for increased liver enzyme levels at a referral center is estimated to be 160 per 100,000.[99]

## Liver Cancer

### Hepatocellular Carcinoma

Patients with cirrhosis from any etiology are at high risk for HCC, with an annual incidence ranging from 1% to 4%.[100-102] In 2015, there were an estimated 854,000 incident liver cancer cases (75% increase from 1990) and 810,000 cancer-related deaths worldwide.[103] The most significant increases in liver cancer–related mortality were in North America, Europe, and Australia. Many countries, including China, have experienced a decrease in liver cancer burden as a result of improved HBV vaccination and decreased aflatoxin exposure.[104]

HCC incidence in the United States has been increasing in recent years, but the rate of increase has slowed.[105,106] Based on data from the US Cancer Statistics registry, the age-adjusted incidence of HCC increased from 4.4 per 100,000 in 2000 to 6.7 per 100,000 in

2012.[107] However, the annual increase of 4.5% between 2000 and 2009 slowed to 0.7% per year from 2010 to 2012, suggesting a possible impending plateau of new HCC cases. HCC incidence stratified by age categories showed that increases in HCC incidence were most pronounced in those in the peak HCV cohort (born 1945–1965), and is decreasing among younger individuals and Asian Americans.[107,108] However, observed improvements in HCC incidence related to implementation of HBV vaccination and therapy or HCV treatment programs may be mitigated or even overshadowed in the future by increasing childhood obesity and early onset NASH, and increasing ALD among younger individuals. Finally, HCV therapy is likely to improve survival with cirrhosis, however, these patients remain at persistent risk of HCC.[109]

There also are several notable trends in HCC incidence by race/ethnicity. Age-adjusted incidence rates are higher among Hispanics (6.3 per 100,000) and blacks (5.0 per 100,000) compared with non-Hispanic whites (2.4 per 100,000).[110] HCC incidence also is increasing disproportionately in Hispanics (4.7%/y since 2000) compared with other racial/ethnic groups.[110,111] Furthermore, blacks and Hispanics diagnosed with HCC are less likely to have it detected at an early stage.[112]

There were approximately 150,000 HCC-related deaths (age-adjusted, 2.3 per 100,000) in the United States from 1999 to 2017 (Table 4). Mortality rates in 2017 were highest among males, Asian/Pacific Islanders, and those ages 75 to 84 years. HCC mortality has increased overall (Figure 1) and in nearly every group with the exception of Asian/Pacific Islanders.[2] Racial disparities in HCC mortality persist and studies suggest that this may be related in part to treatment process failures, with lower rates of early detection and lower odds of curative treatment, including liver transplantation, among racial/ethnic minorities compared with non-Hispanic whites.[112]

## Complications of Chronic Liver Disease and Cirrhosis

### Hepatic Decompensation

As CLD progresses, patients develop complications of hepatocellular dysfunction and portal hypertension that contribute to liver-related morbidity and mortality.[113] Approximately 4% to 12% patients with cirrhosis develop at least 1 decompensating event annually, and the most common decompensating events are ascites, variceal hemorrhage, and hepatic encephalopathy.[70,114–117] As many as 40% of patients with cirrhosis will develop hepatic encephalopathy within 5 years of observation.[118] The presence of these complications are important prognostic indicators, with significantly increased mortality in decompensated compared with compensated cirrhosis.[119,120] Decompensation events also require significant health care utilization: hepatic encephalopathy and ascites/spontaneous bacterial peritonitis each accounted for 59,000 Emergency Department visits in 2014.[121]

### Infection

Patients with cirrhosis have a significantly increased risk of sepsis and infection-related mortality, likely as a result of immune dysfunction, changes in gut microbiota, and bacterial translocation.[122] Among hospitalized patients, the prevalence of bacterial infections ranges from 25% to 50%, with wide regional variability in the type and microbiology of infections.[123] There is a high prevalence of multidrug-resistant bacteria in infected cirrhosis patients (34%), with the highest prevalence in India (73%).[123]

### Acute Kidney Injury

Acute kidney injury (AKI) is common in patients with cirrhosis, particularly those with ascites.[113,124] The physiology of portal hypertension increases the risk of AKI owing to splanchnic vasodilation and decreased intravascular blood volume with resulting renal vasoconstriction. Hepatorenal syndrome, the abrupt and severe form of AKI that occurs in the absence of nephrotoxic medications and shock and despite a trial of volume explanation, portends the worst prognosis.[124,125] Among patients with ascites followed up prospectively, AKI ultimately will develop in half, with a 1-year probability of 24%.[126] AKI has been reported in approximately 20% of all hospitalized patients with cirrhosis and is more common in those with ascites, spontaneous bacterial peritonitis, and gastrointestinal bleeding.[127,128] The burden of hepatorenal syndrome has changed somewhat as definitions have evolved; its annual incidence ranges from 8% to 18%, and 13% to 27% of patients with AKI qualify as having hepatorenal syndrome.[126,129,130]

### Frailty

Physical frailty is common in cirrhosis owing to muscle wasting and poor nutrition. Frailty in those with liver disease is a strong predictor of mortality independent of traditional prognostic tools such as the Child–Pugh score and Model for End-Stage Liver Disease.[131] Frailty can be assessed in a number of ways including grip strength, chair stands per second, gait speed, balance time, and activities of daily living.[132,133] Cirrhosis-related frailty, especially in combination with cognitive dysfunction or psychoactive medications, increases the risk of falls and decreases health-related quality of life.[134–137] Estimates of its burden are highly variable because of heterogeneity in case definitions, but

**Table 4.** Potential Data Sources for Liver Disease Epidemiologic Research

| Data source | Country/region | Strengths | Weaknesses |
|---|---|---|---|
| NHANES | United States | Nationally representative sample of noninstitutionalized individuals<br>Cirrhosis definition is based on interview, examination, and laboratory data<br>Provides estimates of undiagnosed cirrhosis | Cross-sectional design<br>Small sample size (~5000)<br>Potential for selection bias<br>Potential misclassification of mild liver disease |
| VA | United States | Large sample size<br>Includes clinical notes, laboratory data, and imaging<br>Well-validated ICD coding strategies for liver disease and its associated complications | Predominantly male population<br>VA enrollees may differ from general population regarding access or delivery of care<br>Limited information on care received outside VA system |
| Medicare | United States | Large sample size<br>Nationally representative of population age ≥65 years<br>Patients followed up until death | No laboratory data available<br>Relies on diagnosis and procedure codes alone and is subject to misclassification |
| Medicaid | United States | Large sample size<br>Includes sample of patients with low socioeconomic status | No laboratory data available<br>Relies on diagnosis and procedure codes alone and is subject to misclassification |
| Private-insurance claims data | United States | Large sample size<br>Nationally representative of privately insured population | Unable to ascertain death<br>Enrollment relies on ongoing insurance coverage<br>No laboratory data available<br>Relies on diagnosis and procedure codes alone and is subject to misclassification |
| NIS | United States | Large sample size<br>Nationally representative sample of inpatient population<br>Includes all payers | No laboratory data available<br>Relies on diagnosis and procedure codes alone and is subject to misclassification<br>Inability to link hospitalizations to individual patients limits longitudinal follow-up after discharge |
| NRD | United States | Large sample size<br>Accurate assessment of patient readmission | No laboratory data available<br>Unable to account for events that may preclude readmission (eg, death)<br>Relies on diagnosis and procedure codes alone and is subject to misclassification |
| MEPS | United States | Nationally representative of noninstitutionalized individuals<br>Includes health care expenditures from all payers | Potential for recall bias<br>Subgroup analyses among certain groups (eg, race/ethnicity minorities) may not be possible |
| SEER program | United States | Includes information on clinical information, tumor stage at diagnosis, first treatment, and survival<br>Allows linkage to Medicare | Unable to determine etiology or severity of liver disease<br>May not be entirely representative of United States given that it only covers a selected subset of the population<br>Generalizability for Medicare-linked data limited by age of enrollees (age, ≥65 y) |
| US Cancer Statistics registry | United States | Nationally representative data source on HCC incidence from all 50 states (~97% of population) | Unable to determine etiology of liver disease owing to lack of laboratory data<br>Unable to determine HCC stage at diagnosis |
| OPTN | United States | Granular data on waitlisted individuals, liver transplantation, and post–liver transplant outcomes<br>Linked by UNOS to social security death index | Potential for selection bias by transplant centers |
| National patient registries | Denmark, Finland, Iceland, Norway, Sweden | Longitudinal, nationwide clinical data with individual-level linkage<br>Includes detailed information on clinical characteristics, laboratory data, imaging, procedures and outcomes | Resource-intensive |
| CPRD | United Kingdom | Nationally representative data<br>Granular data on diagnoses and prescriptions of patients seen by participating providers | Covers only a subset of the population<br>Longitudinal follow-up evaluation depends on ongoing treatment by a participating practice<br>Limited data on liver-specific information |

**Table 4.** Continued

| Data source | Country/region | Strengths | Weaknesses |
|---|---|---|---|
| ELTR | Europe | Large sample size (155 centers from 28 countries)<br>Standardized questionnaire used<br>Detailed information on liver transplant indications, transplant types, and complications | Potential for misclassification owing to inaccurate completion of questionnaire<br>No information on patient ethnicity or socioeconomic information |
| NORDCAN database | Denmark, Finland, Faroe Islands, Greenland, Iceland, Norway, Sweden | Population-based incidence, prevalence, and mortality data for HCC<br>Longitudinal data allows for examination of HCC trends | Inclusion of only Nordic countries limits generalizability, particularly to racial/ethnic minorities |
| GBD project | Worldwide | Captures data from a wide range of sources to estimate incidence, prevalence, and mortality from liver disease and HCC | Data quality highly variable, particularly in resource-limited areas<br>In many areas, relies on verbal autopsy (post-mortem interview with relatives and/or witnesses of death) |

CPRD, Clinical Practice Research Datalink; ELTR, European Liver Transplant Registry; GBD, Global Burden of Disease; HCC, hepatocellular carcinoma; ICD, International Classification of Diseases; MEPS, Medical Expenditure Panel Survey; NHANES, National Health and Nutrition Examination Survey; NIS, National Inpatient Sample; NRD, National Readmissions Database; OPTN, Organ Procurement and Transplant Network; UNOS, United Network for Organ Sharing; VA, Veterans Affairs.

the reported prevalence of frailty among patients on the liver transplant waitlist ranges from 17% to 43%, and is more common among older patients and those with NAFLD.[133,138]

### *Acute-on-Chronic Liver Failure*

Acute-on-chronic liver failure (ACLF), defined as deterioration of liver function and extrahepatic organ failure, is an increasingly recognized entity associated with considerable morbidity and mortality.[139,140] Definitions for ACLF are heterogeneous, with some based on physiologic markers of end-organ dysfunction and others based purely on clinical assessments of organ failure (coma, hemodialysis, mechanical ventilation).[141] Algorithms for use in administrative data have been used but have never been validated. The prevalence of ACLF is reported to range from 24% to 40% among hospitalized patients with cirrhosis.[139,142,143] In a large cohort of US veterans with ACLF, deaths occurred in 26% and 40% of patients at 1 and 3 months, respectively.[143] In a multicenter European cohort defining and grading ACLF based on the sequential organ failure assessment, 28-day mortality was approximately 30% and ranged from 22% to 77%, depending on the number of organs affected.[139,144]

## Health Care Utilization, Direct Costs, and Disability for Chronic Liver Disease and Cirrhosis in the United States

### *Health Care Utilization*

In the United States in 2014, CLD accounted for more than 1,000,000 outpatient and 325,000 Emergency Department visits (40% increase in Emergency Department visits since 2006).[121] Cirrhosis-related hospitalizations have increased every year between 2001 and 2011, with these increases outpacing both congestive heart failure and chronic obstructive pulmonary disease.[145,146] Inpatient care, which comprises approximately 40% of all costs, accounts for the majority of expenditures in CLD.[147] Annual inpatient costs for cirrhosis patients increased from $4.8 billion ($13,079 per hospitalization) to $9.8 billion ($15,193 per hospitalization) from 2001 to 2011 and a similar economic burden has been demonstrated in CLD.[145,147] Readmissions are common (25.8% at 30 days),[148] conditional on the severity of liver disease,[149] and are particularly related to hepatic encephalopathy and alcohol-use disorder. There are several ongoing efforts to reduce readmissions in the future, although few have proven successful to date.[150,151] In addition to inpatient costs, overall annual health care costs from CLD were $29.9 billion overall, with 3.5-fold higher per-patient costs among patients with ACLF.[145,147]

### *Disability and Health-Related Quality of Life*

CLD also is associated with disability and significant decreases in health-related quality of life.[52,152,153] Compared with age-matched controls, CLD patients have higher levels of unemployment (65.3% vs 31.4%), inability to work as a result of disability (30.5% vs 6.6%), and reported days of disability per year (10.2 vs 3.4).[147] Among individuals age 65 years and older with cirrhosis, approximately 1 in 4 report their health as poor, and 40% have at least 1 impaired activity of daily living.[136] Decrements in health-related quality of life can be seen in CLD even without cirrhosis;

however, health-related quality of life is lowest in those with cirrhosis complications including hepatic decompensation.[154]

## Directions for Future Research

Complicating our knowledge of the present burden of disease is the lack of prospective national registries, and our reliance on variable definitions of CLD in administrative data.[155] Existing data sources for identifying burden and trends in CLD each have unique strengths and limitations and there is ample opportunity for improvement (Table 4). Prospective population-based patient registries, such as the Danish National Patient Registry, serve as benchmarks for epidemiologic data sources.[156] Although resource-intensive, these can yield invaluable findings on the incidence, prevalence, natural history, and real-world treatment of CLD.[89,157,158]

In the United States, although comprehensive national registries are lacking, there have been efforts to prospectively track specific liver diseases and complications of cirrhosis. For instance, a multisite Cirrhosis Quality Collaborative, funded by the American Association for the Study of Liver Diseases, has set out to track patient-reported outcomes in cirrhosis and define standard processes of care and quality metrics.[159] There are several specific areas in need of higher quality data such as ALD, its burden likely is underestimated owing to late referral of patients with liver disease and under-reporting of alcohol use.[78]

Finally, the paucity of reliable data on CLD in many developing nations cripples efforts to improve care.[6] This could be addressed by building infrastructure to define, track, and manage cirrhosis through global partnerships. The World Health Organization, for instance, has announced plans to establish centers of excellence to improve data collection on CLD and HCC throughout the world.[160] In addition, global surveillance of CLD could be improved by emulating existing models in cancer, for which international registries have been immensely important for research on epidemiology, interventions, and outcomes.[161]

## Conclusions

Recent data have shown that the burden of CLD, cirrhosis, and its complications remains substantial. Improvements in the prevalence and outcomes of viral hepatitis contrast with adverse trends in the prevalence and complications of alcohol-related and nonalcoholic fatty liver diseases. Investment and innovation are vital to maintain adequate surveillance of CLD and develop strategies to reduce its burden. Liver disease, liver cancer, viral hepatitis, organ transplantation, obesity, and alcohol use all are projected to have decreases in National Institutes of Health funding, which may hamper these efforts.[121] Continued attempts to track the burden of liver disease will help identify priorities for clinical care improvements, research investment, and health policy initiatives.

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**Conflicts of interest**
These authors disclose the following: Amit Singal has received grant funding from AbbVie and has served on advisory boards for Gilead and AbbVie; and Elliot Tapper has received grant funding (to the University of Michigan) from Gilead and Valeant, consulted for Novartis and Allergan, and has served on advisory boards for Salix/Bausch and Mallinckrodt. The remaining author discloses no conflicts.

**Funding**
This research was supported in part by National Institutes of Health grant T32 DK007634 (A.M.). Dr. Singal's research is supported by National Institutes of Health grantsU01CA230694 and R01MD12565. Also supported by the National Institutes of Health through the Michigan Institute for Clinical and Health Research (KL2TR002241 to E.T.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.